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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 91N-100H
Folic acid (dietary supplement vs food form) and neural tube defects

The Council for Responsible Nutrition (CRN) has participated at every stage of the extensive FDA proceedings relating to a health claim regarding the relationship between folic acid and the reduced risk of neural tube birth defects. CRN is a trade association representing approximately 100 companies in the dietary supplement industry.

In the Federal Register of September 8, 1999, FDA requested additional information and views, in preparation for the agency's further evaluation of this health claim. At issue is the relative effectiveness of synthetic folic acid as compared to food folate and of 0.8 mg as compared to 0.4 mg of folic acid. At the present time, FDA's regulation on the folic acid health claim (21 CFR 101.79) identifies folate and folic acid as equal and interchangeable terms for the nutrient that is the subject of the claim and forbids any statement that a specified amount of folate per serving from one source is more effective than a lower amount per serving from another source.

The court's January 1999 decision in ***Pearson v.*** *Shalala* requires FDA to reconsider whether to permit a claim that "0.8 mg of folic acid in a dietary supplement is more effective in reducing the risk of neural tube defects than a lower amount in foods in common form."

CRN urges FDA to amend the folic acid health claim regulation to permit the statement that experts recommend that women of childbearing age get 0.4 mg of synthetic folic acid daily, in addition to the folate that occurs naturally in their diets. In 1998, the Institute of Medicine published new Dietary Reference Intakes for several B vitamins, including folic acid, and specifically recommended: "In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 mcg of synthetic folic acid from fortified foods and/or supplements in addition to intake of food folate from a varied diet." This is important information which should be conveyed in the context of the folic acid health claim. Products eligible to use this aspect of the claim should be limited to dietary supplements and fortified foods providing at least 0.4 mg (400 mcg) of folic acid. We recognize that, under the existing regulation, products providing more than 0.4 mg (or 0.8 mg in the case of products represented for use by pregnant or lactating women) would need to include a statement identifying 1 .O mg as the safe upper limit. As recognized by the Institute of Medicine in publishing the new Dietary Reference Intakes for B vitamins, the evidence for an upper limit for folic acid is limited and is based on the potential for masking B-12 deficiency. That publication establishes a LOAEL (Lowest Observed Adverse Effect Level) of 5.0 mg for folic acid, and then applies an uncertainty factor of 5 to arrive at an Upper Limit (UL) of 1 .O mg. It goes on to observe: "In general, the

prevalence of vitamin B-12 deficiency among females in the childbearing years is very low, and the consumption of folic acid at or above the UL in this subgroup is unlikely to produce adverse effects."

The March of Dimes is currently leading a national campaign on folic acid, in cooperation with the Centers for Disease Control and Prevention (CDC) and more than 20 other cooperating associations of health care professionals. Central to the message of the campaign is the advice that all women of childbearing age should take a multivitamin containing 0.4 mg of folic acid daily, in addition to eating more foods rich in folate and consuming products fortified with folic acid. It would be appropriate for health claims about folic acid to reinforce this message.

CRN believes it also would be appropriate to reconsider the current eligibility requirements for conventional foods that may bear the folic acid claim. The regulation currently permits conventional foods with 10% or more of the RDI for folic acid to bear the claim, in order to allow most fruits and vegetables to be eligible. This policy fails to identify for consumers those foods that are rich in dietary folate. Indeed, CRN believes the current eligibility provisions for conventional foods could provide consumers with misleading information, by permitting the claim to appear on foods that are not rich in folate. At a minimum, we urge FDA to raise the eligibility requirement for conventional foods to 20% of the RDI for folate. This would be consistent with the general requirements for health claims (10 1.14), which state that in order to qualify for a health claim based on providing more of any substance, foods should be "high" in that substance. In the case of vitamins and minerals, the term "high" is reserved to foods that provide 20% or more of the Reference Daily Intake.

CRN does not believe the data support a statement that 0.8 mg of folic acid is more effective than lower intakes (specifically 0.4 mg) in reducing the risk of neural tube birth defects. Intervention trials for preventing the recurrence of neural tube birth defects, epidemiological studies, and a large recent public health study all indicate that supplementation with about 0.4 mg of folic acid is as effective as supplementation with larger amounts. The Smithells studies on reducing the risk of recurrence utilized a multivitamin providing 360 mcg of folic acid per day (120 mcg three times daily) and showed benefits equivalent to the MRC trial utilizing an eleven-fold higher level of 4 mg of folic acid per day. The substantial body of epidemiological evidence shows a protective effect of periconceptional use of multivitamins, which commonly provide 0.4 mg of folic acid per day. The results of a large public health intervention in China were published just this month, showing dramatic protective effects of 0.4 mg of folic acid daily. These supplements reduced the risk of neural tube defects by 85% in a high-risk region and by 40% in a lower-risk region of China. The Czeisel study in Hungary used multivitamins providing 0.8 mg of folic acid per day in the form of a multivitamin, and also reported significant protection against neural tube defects. In the Hungarian study, there were no neural tube birth defects in the treated group, but the number of birth defects in the unsupplemented group was small. CRN does not believe the evidence as a whole supports the hypothesis that 0.8 mg is more effective than 0.4 mg.

CRN appreciates the opportunity to submit comments on this important issue. We believe it is critically important to utilize all available resources to get the message to women of childbearing age that it is possible to dramatically reduce the number of babies born each year with crippling or fatal neural tube defects, through the simple expedient of

taking a multivitamin providing 0.4 mg of folic acid daily. It is estimated that about 2500 babies are born every year with these birth defects. Another 1500 pregnancies, every year, result in miscarriages or stillbirths due to neural tube birth defects. All 4000 of these tragedies bring grief and suffering to the families involved. The Centers for Disease Control and Prevention (CDC) and the March of Dimes estimate that 50 to 70 percent of these birth defects can be avoided, if women of childbearing age get adequate intakes of folic acid, before they become pregnant and during the first trimester. The national campaign on folic acid advocates that women take a daily multivitamin supplement and eat a healthy diet, including foods fortified with folic acid and foods naturally rich in folic acid. By amending the folic acid health claim to permit a statement about the importance of synthetic folic acid and by raising the qualifying level of folate in conventional foods, FDA can help women identify the products most likely to help them achieve a protective folic acid intake. We urge the agency to move promptly to implement these changes.

Sincerely,

A Dickinson

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